PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220 4/4

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/005421	22.12.2004	22.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07C405/00, C07C59/90, A61K31/5575, A61K31/192, A61P37/00

Applicant
PHARMAGENE LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Goetz, G Telephone No. +49 89 2399-8105

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005421

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9, 10, 15 - 18

because:

☒ the said international application, or the said claims Nos. 9, 10, 15 - 18 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005421

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10,14,18
	No:	Claims	11,13,15,17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-8,11-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

D1: SZCZEPAN JOZEFOWSKI ET AL.: "Exogenous but not endogenous prostanoids regulate cytokine secretion from murine bone marrow dendritic cells: EP2, DP, and IP but not EP1, EP3, and FP prostanoid receptors are involved" INTERNATIONAL IMMUNOPHARMACOLOGY, vol. 3, 1 June 2003 (2003-06-01), pages 865-878, XP002325093

D2: NIALS A T ET AL: "AH13205, A SELECTIVE PROSTANOID EP2-RECEPTOR AGONIST" CARDIOVASCULAR DRUG REVIEWS, NEVA PRESS, BRANFORD, CT, US, vol. 11, no. 2, 1993, pages 165-179, XP009004866 ISSN: 0897-5957

D3: VANCHERI C ET AL: "The lung as a privileged site for the beneficial actions of PGE2" TRENDS IN IMMUNOLOGY, ELSEVIER, CAMBRIDGE, GB, vol. 25, no. 1, January 2004 (2004-01), pages 40-46, XP004481206 ISSN: 1471-4906

D4: KANDA N ET AL: "Prostaglandin E2 suppresses CCL27 production through EP2 and EP3 receptors in human keratinocytes" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, vol. 114, no. 6, December 2004 (2004-12), pages 1403-1409, XP004666387 ISSN: 0091-6749

D5: HILLOCK C J ET AL: "INHIBITORY PROSTANOID EP RECEPTORS IN HUMAN NON-PREGNANT MYOMETRIUM" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 378, no. 1, 28 July 1999 (1999-07-28), pages 99-108, XP001124311 ISSN: 0014-2999

D6: WO 03/037433 A (ALLERGAN, INC) 8 May 2003 (2003-05-08)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. For the assessment of the present claims 9, 10, 15 to 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however,

claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. D1 discloses the effect of EP_2 receptor agonists (PGE2, butaprost) on different mediators involved in inflammatory diseases. In particular D1 discloses the effect of EP_2 receptor agonists (PGE2, butaprost) on the release of TNF-alpha which is inhibited by these substances (see abstract, see paragraph 3.3).
   D2 discloses the effect of AH13205 and butaprost on mediator release from inflammatory cells. In particular it is disclosed in D2 that the release of mediators is inhibited (see last paragraph of D2).
   The subject matter of present claims 11, 13 15 and 17 is thus not novel over the disclosure of D1 and D2 (PCT Article 33.2).

2. Due to the antiinflammatory effect of PGE2, butaprost and AH13205 as disclosed in D1 and D2 the use of these compounds in the treatment of psoriasis (which is an inflammatory disease) is not considered to involve an inventive step.
   The subject matter of present claims 11 to 13,15 to 17 is thus not based on an inventive step (PCT Article 33.3).

3. The documents D 5 and D6 disclose the compound AH13205 which acts as an agonist of the EP2-receptor.
   The underlying problem can be seen in the provision of the single stereoisomers of this compound which can then be used as agonists of the EP2-receptor.
   The stereoisomers as mentioned in claim 1 are presented as being the solution to this problem.
   Although these two isomers are not described in the prior art, an inventive step is missing: It is known that AH13205 acts as an agonist of the EP2-receptor. It is considered to be obvious for the skilled person to separate the isomers of a racemate

which is known to be pharmacologically active. This procedure has been done by present application.
Furthermore, it is not apparent, if the two isomers have been isolated since in the examples not the isolated isomers are mentioned but "mixtures" are mentioned instead. In the absence of further evidence the underlying problem as defined above cannot be considered as being solved by present application.
In the absence of a solution, however, no inventive step can be acknowledged for the subject matter of claims 1 to 10, 14 and 18 (PCT Article 33.3).

4. Industrial applicability can be acknowledged for claims 1 to 8, 11 to 14 (PCT Article 33.4).

Re Item VI
Certain documents cited

1. The documents D3 and D4 disclose that EP2 receptor agonists are inhibitors of the release of inflammation mediators and can be used in the treatment of immunological disorders such as psoriasis and inflammatory lung diseases
(see present claims 11 to 13 and 15 to 17).

Re Item VIII
Certain observations on the international application

1. The subject matter of present claims 1 to 3 is directed to compounds (isolated stereoisomers).
According to the examples not the isolated stereoisomers are prepared but a "mixture" instead.
This information (examples) is not considered to represent a disclosure which is sufficiently clear and complete for the invention to be carried out by a person skilled in the art.
The subject matter of present claims 1 to 18 is thus considered not to meet the

requirement of Article 5 PCT.

2. The characterisation of a compound as being "a chemically protected form" or "a prodrug thereof" is considered not to be clear in the sense of Article 6 PCT: a chemical compound has to be unambiguously defined by structural features.